1025 – RIBOSOMES AS DETERMINANTS OF CELL IDENTITY AND FUNCTION

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For decades, it has been thought that, across a given organism, all ribosomes are alike, and that from the perspective of the ribosome, translation is a passive "mRNA-in, protein-out" process. However, through various studies, it is now becoming clear that ribosomes are actually a heterogeneous pool of complexes, with diverse tissue-specific compositions and diverse translational properties. However, the role of ribosome heterogeneity in dictating biological and physiological processes is obscure.
Using RNA modification sequencing techniques, we focused on specific hematopoietic stem and progenitor cells (HSPCs) compartments and mapped their 2'-O-methylation and Pseudourine profiles. We demonstrate cell-type-specific rRNA modification profiles in the HSPCs compartments, revealing specific rRNA modifications with potential as translation regulators. We identify specific modification sites which are essential for the maintenance of stem properties. Using CRISPR screen we also find specific 2'-O-methylations sites essential for erythroid differentiation. Our study demonstrates the active role of the ribosome and of translation in dictating cell fate.

1026 – REWIRING OF TRANSCRIPTION FACTOR NETWORKS DURING THE FETAL TO ADULT TRANSITION IN HSCS

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Many blood diseases are biased in their age of onset. This occurs in concert with underlying changes in the properties of hematopoietic stem and progenitor cells (HSPCs) over the course of development, maturation, and aging that tailor the output of mature blood cells to age-specific physiology. Understanding how blood formation changes over the course of a lifetime would form a foundation upon which to investigate age-related determinants of manifestations of blood diseases. In previous work, we found that the Polycomb repressive complex 1 component Cbx2 is a downstream target of the heterochronic Lin28b/*let-7* axis that functions to specify the temporal maturation state of definitive HSPCs. We found that the master HSC TF Erg is repressed by Cbx2 in fetal HSPCs. Subsequently, Erg is upregulated during maturation from the fetal to adult HSC state. Moreover, Erg motifs are highly enriched in chromatin regions specifically active in adult relative to fetal HSPCs. These findings suggest heterochronic role(s) for Erg in hematopoiesis. We hypothesized that as a key TF in HSCs, age-related changes in Erg likely impact the developmental state of HSCs. Our approach was to either reduce expression of Erg in adult HSPCs or ectopically activate Erg in fetal HSPCs and determine consequences on function. We found that ectopic expression of Erg in Lin28b-expressing HSPCs reprogrammed to the fetal state blunted fetal lineage biases. In adults, loss of a gene dose of Erg resulted in persistence of hallmarks of the fetal HSC state and fetal-like HSPC distributions into maturity. Early postnatal Erg+/- HSCs do not effectively transition to quiescence and show fetal-like patterns of active self-renewal, which is followed by HSC exhaustion later in adulthood. We find that adult Erg+/- HSPCs ectopically maintain fetal-like gene expression profiles with failure to repress fetal-biased HSC TFs. Overall, these findings demonstrate that master hematopoietic TFs are tightly titrated to implement age-appropriate rates self-renewal and mature cell output in HSPCs.